REMARKS

Status of the claims

Claims 6-16 were previously cancelled without prejudice, claims 1-5 and 17-19 are therefore under examination.

With entry of the instant amendment, claims 1 and 19 have been amended. The amendments to the claims add no new matter and are supported throughout the application as filed. Claim 1 recites selecting at least five mismatched positions in a protein sequence alignment wherein at a mismatched position, the parent protein sequences have different amino acids. Support can be found, *e.g.*, at paragraph 13 and paragraph 57, lines 1-3 with paragraph 73, lines 1-2.

Claim 1 additionally recites determining a minimal nucleic acid coding sequence where, for each mismatched site, the minimal nucleic acid coding sequence comprises a degenerate codon encoding an amino acid residue at the mismatched position, where the degenerate codon comprises at least one degenerate nucleotide position and the presence of the degenerate nucleotide position results in a codon that alternatively encodes the different amino acids at the mismatched positions in the parent protein sequences when the minimal encoding nucleic acid sequence is synthesized. Support can be found, *e.g.*, at paragraph 74 and at paragraph 76..

Claim 1 further recites creating a library comprising 32 or more nucleic acids encoding a plurality of hybrid protein members, wherein the nucleic acids comprise the minimal encoding sequences for the mismatched positions. Support can be found, *e.g.*, at paragraph 83, lines 1-2.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-5 and 17-19 are rejected as allegedly indefinite in the recitation of a number of terms, as follows, in claim 1.

"the parental codon"

The Examiner contends that there is insufficient antecedent basis for "the parental codon" in step (b) as previously amended, and that it had not been established that there is a parental nucleic acid sequence from which codons are determined. In order to expedite prosecution, the claims have been amended.

"a degenerate codon"

The Examiner alleges that the recitation of "a degenerate codon" in step (b) is indefinite because it is not clear if this is intended to be the same degenerate codon as in the first occurrence, or if it is a "second" degenerate codon. In the interest of furthering prosecution, the claims have been amended. It is clear that each codon that encodes the amino acid residue at a mismatched site is a separate codon and not the same degenerate codon as in the first occurrence of a mismatched site.

In addition, the Examiner contends that the term "degenerate codon" as employed in the claims is contrary to the art-accepted definition and therefore is indefinite. Applicant respectfully traverses this rejection. As the Examiner know, Applicants may be their own lexicographers (*e.g.*, MPEP § 22173.01). Here, the meaning of the term "degenerate" is clearly set forth in the specification. For example, in paragraph 74, the specification states that a point of degeneracy is "a point in which nucleotide variation results in codons encoding only one or the other parental amino acid." At paragraph 76, the specification states that "a single nucleic acid degeneracy can encode both amino acids that differ at a particular position in the parent sequences." Thus, in view of the disclosure in the specification, one of skill can readily determine the meaning of "degeneracy" or "degenerate codon" as used in the context of this invention.

Last, the Examiner contends that a sequence is degenerate only if there is another sequence for comparison, and that the claims fail to establish a parent nucleic acid sequence. Although Applicants believe that the claims as previously filed are clear, in order to expedite prosecution, the claims have been amended.

In view of the foregoing, Applicants respectfully request withdrawal of each of the rejections under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph--new matter

Claims 1-5 and 17-19 were rejected as allegedly failing to meet the written description requirement. Specifically, the Examiner contends that step (b) of the claims as previously amended constitutes new matter. The Examiner argues that the specification at paragraph 13 describes that the hybrid proteins will comprise "a minimum of 5 amino acid residue differences", not five degenerate codon positions; and that paragraph 57 discloses that the parent proteins differ by 5 amino acid positions, not the claimed five degenerate codon positions. Although Applicants believe that the previous claim language is fully supported by the description in the specification, in order to expedite prosecution, the claims have been amended. Examples of support for the amendments is provided above in the **"Status of the claims"** section. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102

Claim 1-3 and 5 are rejected as allegedly anticipated by Ness *et al., Nature Biotechnology* 20:1251-1253, 2002. In the interest of expediting prosecution, Applicant submits herewith a Declaration under 37 C.F.R. § 1.131 by Peter B. Vander Horn to overcome the cited reference. Submission of the declaration does not constitute an admission that Applicant concurs with the Examiner's evaluation of Ness *et al.*

The Declaration describes conception of, and reduction to practice of, the claimed invention in the United States, prior to November 2002, the month in which the Ness *et al.* reference was published online. As described by the inventor in the accompanying Declaration, the present invention relates, in part, to methods of generating hybrid proteins. In the methods of the invention, at least two parent protein sequences that have a common biological activity are aligned and positions at which the parent amino acid residues are different are identified (such a position is referred to in the Declaration as a "divergent site"). The codons that encode the differing residues are compared and a nucleic acid sequence encoding a protein that is a hybrid

of the parent proteins is derived. This nucleic acid sequence includes degeneracies at codons that encode divergent sites. Such a degenerate codon has at least one nucleotide position in the codon that is variable such that the codon can encode multiple parental amino acid residues at the divergent site, depending on which nucleotide is incorporated at that codon position during synthesis of a nucleic acid molecule. Libraries can thus be generated in which members are hybrids that have amino acid residues from one of the parents at some of the divergent sites and, independently, amino acid residues from a different parent at other divergent sites. The library is then screened and functional hybrid proteins are identified.

Prior to November 2002, the inventor aligned a parent Pfu polymerase protein sequence and a parent Deep Vent® polymerase protein sequence and identified differences in the amino acid sequences. An *E. coli* codon usage table was used to compare the various codons that can encode the differing amino acids. A nuclei acid sequence that alternatively encoded differing parental amino acid residues at sites of variation in the protein sequences was then created.

Oligonucleotides were designed for synthesis to assemble together to form a full length polymerase gene to make a library encoding hybrid polymerase proteins. A copy of a laboratory notebook page showing the sequences of the oligonucleotides, including the positions that can encode alternative amino acid residues at sites that differ in the parent protein sequences, is provided in Exhibit A of the Declaration. The oligonucleotides were synthesized and assembled by overlap extension.

Functional polymerase proteins encoded by members of the library were then identified. An example of a PCR analysis using an exemplary hybrid polymerase protein that was isolated from the library is shown in the copy of a laboratory note book page provided as Exhibit B of the Declaration. The Exhibit shows a gel with the products of amplification reactions performed using a hybrid polymerase, designated "PhS1". The hybrid polymerase amplified template DNA targets of 4, 5, 9, and 13 kb in length. The gel was obtained prior to November 2002.

In view of the foregoing, Applicant submits that it has been unequivocally established that the claimed invention was conceived of and reduced to practice prior to November 2002. Applicant therefore respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

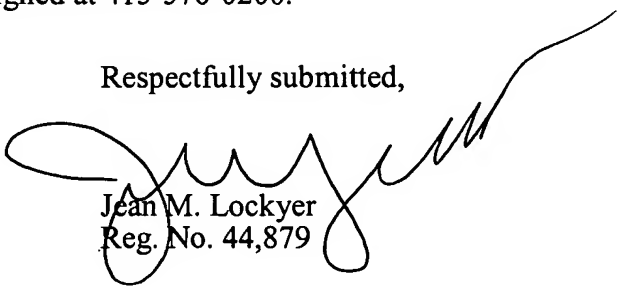
Claims 1-5, 17, and 19 were rejected as allegedly unpatentable over Ness *et al.* in view of Xia *et al.*, *Proc. Natl. Acad. Sci. USA* 99:6597-6602, 2002; and over Ness *et al.*, in view of Xia *et al.* and further in view of Slater *et al.*, U.S. Patent No. 6,077,664. Applicant has demonstrated completion of the invention prior to the November 2002 publication date of Ness *et al.* Because the filing of the Declaration removes Ness *et al.* as prior art against the above-referenced patent application, Ness *et al.* cannot form the basis of an obviousness rejection under 35 U.S.C. § 103. Applicant therefore respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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